New Insights Into Pollution and the Cardiovascular System: 2010 to 2012

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As cited in the recent 2010 American Heart Association scientific statement, the World Health Organization estimated that mass of fine particles <2.5 μm in aerodynamic diameter ($PM_{2.5}$) contributed to ≈800 000 premature deaths per year, ranking $PM_{2.5}$ as the 13th leading cause of worldwide mortality.[1] After an extensive review of studies on the cardiovascular effects of $PM_{2.5}$, designed as a follow-up to a 2004 AHA scientific statement, the 2010 AHA report reached several new conclusions:

- Exposure to elevated levels of $PM_{2.5}$ over a few hours to weeks can trigger cardiovascular disease--related mortality and nonfatal events. The evidence is strongest for ischemic heart disease (IHD) events, including myocardial infarction and heart failure hospitalizations.
- Longer-term exposure (eg, a few years) increases the risk for cardiovascular mortality to an even greater extent than exposure over a few days and reduces life expectancy in more highly exposed populations by several months to a few years.
- Reductions in particulate matter (PM) levels are associated with decreases in cardiovascular mortality within a time frame as short as a few years.
- Many credible pathological mechanisms have been elucidated that support the biological plausibility of these findings. These include systemic inflammation, systemic oxidative stress, thrombosis and coagulation, systemic and pulmonary arterial blood pressure responses, vascular (including endothelial) dysfunction, cardiac ischemia, and heart rate variability/autonomic dysfunction.

The 2010 AHA document and the subsequent review by Sun et al[2] focused on the literature on the mechanisms for cardiovascular effects of pollution and pointed out that there were fewer human studies and less consistency in study results concerning the following:

- Effects of fine particle mass on cerebrovascular and cardiac arrhythmia outcomes.
- Cardiovascular effects of the coarse ($PM_{10-2.5}$) or ultrafine (<0.1 μm) fractions of PM_{10}.
- Cardiovascular effects of pollutants other than particle matter. Specifically, the AHA summary stated, "Although $PM_{2.5}$ mass has rightfully attracted attention as a target for regulation and epidemiological study, more than 98% of the air pollutant mass in the mixture we breathe in urban settings is from gases or vapor-phase compounds such as CO, volatile organic carbons (OCs), NO_2, NO [nitric oxide], O_3, and SO_2."[1] More studies were needed not only on cardiovascular effects of individual gases and OCs but also on effects of particle constituents, as well as pollution mixtures and sources.
- Biological mechanisms for the effects of pollutants on repolarization abnormalities or atherosclerosis. In addition, although not emphasized by the AHA statement, there were also relatively few human studies providing direct evidence for thrombogenicity of pollutants.
- Sources of susceptibility or vulnerability to pollutant effects, including ambient temperature and other meteorologic exposures.

Between 2006 and 2010, the US Environmental Protection Agency (EPA) published Integrated Science Assessments (www.epa.gov/ncea/isa/) summarizing the evidence for health and environmental effects of the 6 criteria pollutants (ozone, particulate mass, carbon monoxide, sulfur oxides, nitrogen oxides, and lead) for which National Ambient Air Quality Standards are set. In our review article, taking the EPA's Integrated Science Assessments and the 2010 AHA scientific statement as our starting point, we provide a selective update on new findings (2010–2012) in human epidemiological and controlled human exposure research that add insight into major areas of uncertainty defined by the AHA on the associations of individual pollutants with cardiovascular and cerebrovascular outcomes. We also extend the AHA 2010 review of potential approaches to protection against the cardiovascular effects of air pollution at the individual, community, and public policy levels.

In our update on cardiovascular effects of gaseous pollutants, we focus on ozone, on which the most controlled human exposure and human epidemiological work has

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been done, to distinguish the specific effects of ozone from effects of particle components and other gases. We review new reports from controlled human exposure studies that assessed the health effects of combinations of >1 pollutant and observational epidemiological studies that put >1 pollutant (particle mass and gases) into their predictive models. However, the definition of clusters of particle constituents and pollution mixtures and the ascertainment of their health effects are beyond the scope of this review. These are currently being actively investigated, in part through currently funded EPA Clean Air Act Centers (www.epa/oar/caa). We also acknowledge that there is a large complementary growing literature that uses in vitro and animal models to evaluate pollution effects; for the most part, that literature is beyond the scope of our review.

Our review includes an update on sources of vulnerability and susceptibility. According to the EPA (2009 Particle Matter EPA Integrated Science Assessment, Chapter 8 [http://www.epa.gov/ncea/isa]),

> …the National Air Quality Standards are intended to provide an adequate margin of safety for both general populations and sensitive subgroups…to facilitate the identification of populations at the greatest risk for PM-related health effects, studies have evaluated factors that contribute to the susceptibility and//or vulnerability of an individual to PM. The definition for both of these terms has been found to vary across studies, but in most instances susceptibility refers to biological or intrinsic factors (eg, lifestage, gender) while vulnerability refers to nonbiological or extrinsic factors.

In this review, vulnerability refers to factors that increase the potential for exposure, and susceptibility refers to individual factors that increase risk at any given level of exposure. Susceptibility implies a greater response at any given level of exposure.

Our literature review is based primarily on 2010 to 2012 PubMed searches using combinations of the following key words: pollution; cerebrovascular, arrhythmia; atherosclerosis; coarse particles; ultrafine particles; OC, ozone, nitrogen dioxides, carbon monoxide, chronic effects; wild fires, biomass; and temperature, susceptibility, vulnerability.

Update, 2010 to 2012: Cerebrovascular Effects of Pollution

The retina affords a view into microvascular changes that may be affected by pollution. After adjustment for multiple potential confounders, the Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated an association between living in a region with higher with increased $PM_{2.5}$ and reduced retinal vessel diameter.[3] Cerebrovascular imaging is needed to evaluate the specific effects of pollution on macrovascular and microvascular disease leading to ischemic stroke and vascular dementia. Because of methodological or technological challenges, including the need for neuroimaging to identify the presence of subclinical disease and the difficulty of assessing the timing of stroke onset in studies based on administrative data,[4] the relation of air pollution exposures to the risk of acute or chronic cerebrovascular outcomes has been less thoroughly examined than the relation of pollution to other cardiovascular outcomes. Many studies have used administrative data sets that are subject to misclassification of specific outcome diagnosis and the timing of stroke onset[4] and do not lend themselves to the evaluation of biological mechanisms for the relation of pollution or pollutant components to cerebrovascular outcomes. These studies have been reviewed recently in a new report showing that the estimated odds ratio of ischemic stroke onset was 1.34 (P<0.001) after a 24-hour period classified as moderate ($PM_{2.5}$, 15-10 µg/m^3) by the US EPA's Air Quality Index compared with a 24-hour period classified as good ($PM_{2.5}$ <15-10 µg/m^3; the Figure).[5]

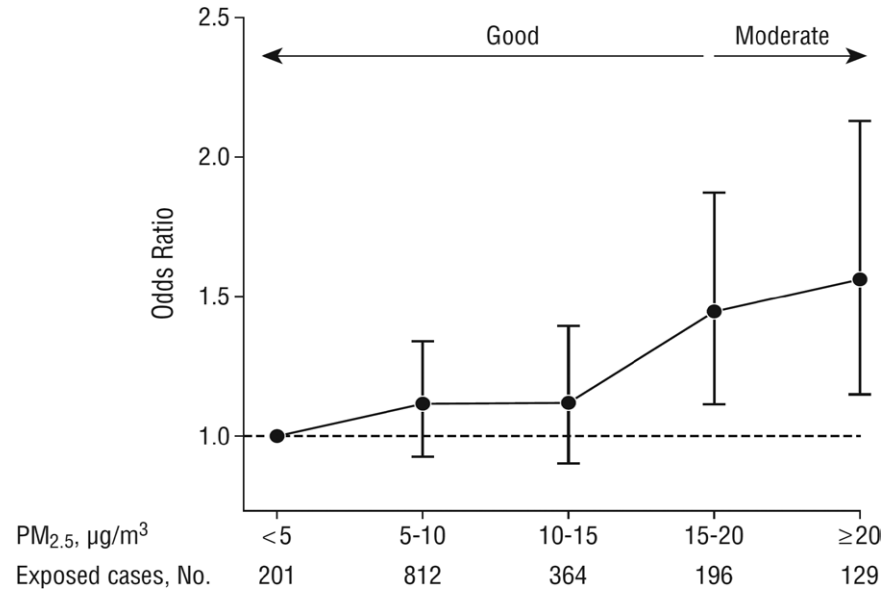

Figure. Odds ratio of ischemic stroke onset for US Environmental Protection Agency categories (good and moderate) of mean ambient fine particulate matter air pollution ($PM_{2.5}$) levels in the 24 hours preceding stroke onset. Error bars indicate 95% confidence interval. Reproduced from Wellenius et al[5] with permission from the publisher.

Table. Update, 2010 to 2012: Cardiovascular Effects of Short-term and Long-term Exposures to Ozone, Other Gaseous Pollutants, and Organic Carbon

Population	Study Design/Statistical Methods	Exposures	Findings
64 Adults with type 2 diabetes mellitus or glucose intolerance; 46 selected on basis of genetics[16]	Repeated measures; 363 ECG recordings	Short-term O_3, SO_4, UFP	Increase in heart rate and T-wave complexity with 1- to 4-h increases in O_3, even with adjustment for particle levels
23 Healthy adults[17]	Controlled human exposure;randomized crossover	2-h of clean air or 0.3 ppm O_3 while intermittently exercising	Increase in interleukin-8; decrease in plasminogen activator inhibitor-1;increase in QT interval; decrease in high-frequency component of heart rate variability
70 Adults with type 2 diabetes mellitus[18]	355 Repeated measures	Short-term O_3, $PM_{2.5}$, SO_4, BC, OC, PNC	Increase in BP with increased 5-d mean $PM_{2.5}$, BC, OC; lower BP with increased 5-d mean O_3
Population-based study of 5594 subjects 6–79 y of age in the Canadian Health Measures Survey[19]	Cross-sectional	Short-term O_3, $PM_{2.5}$, NO_2	Increased BP and heart rate; reduced lung function and exercise tolerance with higher O_3 levels on day of survey; BP also increased with higher NO_2, and $PM_{2.5}$; no multiple pollutant models
Population of Dijon, France (≈150 000), 2001–2007[20]	Case-crossover	Short-term O_3; $PM_{2.5}$, SO_2, CO, NO_2	Increased ischemic cerebrovascular events and myocardial infarction in vulnerable subpopulations with 1- to 3-d O_3; no other pollutant associations
2 Municipalities in Po Valley, Italy[21]	Time series: relative risk of annual mortality estimated from administrative data	O_3, NO_2 (1-h/8-h average); PM_{10} (24-h average)	Increased overall and cardiovascular mortality with increased O_3, NO_2, PM_{10}; no adjustment for potential confounders or multiple-pollutant models
Population of Seoul, South Korea[22]	Time stratified case-crossover	24-h average O_3, NO_2, PM_{10}, SO_2, CO	Increased cardiovascular mortality with increased NO_2, PM_{10}, SO_2, CO, adjusted for weather parameters; no multiple pollutant models; manual laborers at higher risk than professionals
Population of Suzhou, China[23]	Time series	2-d average of maximum 8-h average O_3	Increased cardiovascular mortality with increased O_3; associations stronger in cool weather
Population of Prague (≈1 200 000)[24]	Time series	Short-term O_3, PM_{10}	Increased respiratory, but not cardiovascular mortality with increases in 1-d lagged O_3; results not confounded by PM_{10}
4 Cities in Pearl River Delta, China[25]	Time series 2006–2008	Short-term O_3, NO_2, PM_{10}	Previous 2-d average O_3 or NO_2 predicted increased cardiovascular mortality; results not confounded by PM_{10}
Lisbon, Portugal[26]	Time series 2004–2006	Short-term O_3, $PM_{2.5}$	Independent associations of short-term O_3 and $PM_{2.5}$ with cardiovascular mortality; elderly more susceptible
10 Italian cities; 276 205 deaths, 2001–2005[27]	Time stratified case-crossover	Short-term O_3, NO_2, PM_{10}	Increased cardiac mortality with daily average NO_2,associations independently of O_3, PM_{10}
Large urban populations from 4 Asian countries (Bangkok, Thailand; Hong Kong; Shanghai, China; Wuhan, China)[28]	Time series	Short-term O_3, NO_2, SO_2, PM_{10}	With exception of NO_2 in Wuhan, associations of pollution with cardiovascular mortality greatest in Bangkok
8960 High-risk infants, 1998–2002[12]	Time series	Short-term O_3, NO_2, CO, SO_2, PM_{10}, $PM_{2.5}$, EC, OC	Increased bradycardia with increased 2-d averaged maximum O_3 and NO_2
≈100 000 Participants, California Teachers Study[29]	Cox proportional hazards model	Long-term O_3, PM_{10}, $PM_{2.5}$, NO_2, NOx, CO, SO_2	$PM_{2.5}$ strongly correlated with all pollutants other than SO_2; increased long-term $PM_{2.5}$ and PM_{10} associated with increased IHD mortality and incident stroke in single- and multiple-pollutant models; NOx, NO_2, O_3 predicted IHD mortality only in single-pollutant models before adjustment for PM
Metropolitan Vancouver; 5-y exposure with 4-y follow-up[30]	Cox proportional hazards model	Annual average BC, $PM_{2.5}$,NO, NO_2 during 5-y exposure period	Increased coronary heart disease hospitalization with increased BC after adjustment for SES variables, $PM_{2.5}$, and NO_2
Residents of Shenyang, China[31] (1998–2009)	Retrospective cohort study; Cox proportional hazards model	Annual average PM_{10}, SO_2, NO_2	Increased annual average PM_{10} or NO_2 associated with increased cardiovascular and cerebrovascular mortality; no multipollutant models presented
Cohort of 2360 pulmonary clinic patients, Toronto, Canada, enrolled 1992–1999[32]	Poisson regression estimating relative risk	Estimated residential annual NO_2; regional mean O_3 and $PM_{2.5}$	NO_2, but not O_3, or $PM_{2.5}$ were associated with increased risk of IHD
38 Adults with coronary artery disease[33]	Repeated measures	Short-term size-fractionated PM; OC, O_3, PNC, NO_2, NOx	ST-segment depression with 1-h to 4-d averages of "combustion-related aerosols and gases" but not "secondary (photochemically aged)" organic aerosols or ozone

BC indicates black carbon; BP, blood pressure; IHD, ischemic heart disease; NO, nitric oxide; NOx, nitrous oxide; OC, organic carbon; PM, particulate matter; PNC, particle number concentration; and SES, socioeconomic status.

The increased risk was greatest within 12 to 14 hours of exposure.

Update, 2010 to 2012: Cardiac Arrhythmia, Arrhythmia Precursors, and Pollution

Evidence continues to be mixed for associations between pollution and documented cardiac arrhythmias or electrophysiological changes such as repolarization abnormalities that may increase the risk of arrhythmias. Even more so than studies of stroke, ascertainment of the timing of the onset of the outcome and the specific electrophysiological nature of the outcome can be challenging to ascertain without personal monitoring, which is absent in studies of administrative data sets, which often report null findings.[6] In their recent review, Link and Dockery[7] concluded that "the incremental risk of air pollution in triggering arrhythmias… is greatest for patients with underlying cardiac disease." A London study examined associations of 11 pollutants with activation of implanted cardioverter-defibrillators, finding mostly weak associations with the elevation of a number of secondary regional pollutants, the strongest of which was the nontraffic particle component sulfate.[8] Increases in premature ventricular counts, atrial fibrillation/flutter, and its precedent, P-wave complexity, were associated with increased $PM_{2.5}$ in the previous 1 to 2 hours in a Pennsylvania study of 105 middle-aged healthy nonsmokers with 24-hour ECG and personal particle monitoring.[9,10] Ghio et al[11] presented a case report of new-onset atrial fibrillation that occurred 20 minutes into a controlled exposure to concentrated ambient particles and resolved within 2 hours with no sequella. In studies of vulnerable populations who have personal electrophysiological monitoring, ozone has also been considered a risk factor for arrhythmias. An increase in the maximum ozone level predicted increases in bradycardia and apnea in high-risk infants on home monitors.[12]

Controlled human exposure to 1-hour exposures of diesel exhaust did not influence heart rhythm or variability in a UK study.[13] Increased spatial dispersion of myocardial repolarization, but not T-wave alternans, was seen after controlled human exposures to concentrated ambient particles, ozone, or a combination of the 2 exposures.[14] Increases in long-term estimated residential $PM_{2.5}$ predicted increased odds of QT prolongation without overt ventricular abnormalities in the Multi-Ethnic Study of Atherosclerosis (MESA).[15] Two recent studies (the Table) also suggest acute effects of O_3 on repolarization abnormalities in sensitive subjects.[16,17]

Update, 2010 to 2012: Cardiovascular Effects of the Coarse ($PM_{10-2.5}$) or Ultrafine (<0.1 μm) Fractions of PM_{10}

Findings on cardiovascular health effects of coarse or ultrafine particles remain relatively sparse. A recent study of patients undergoing cardiac rehabilitation showed associations of ambient ultrafine particles with subclinical ECG and blood pressure outcomes, but in multiple-pollutant models, the ultrafine particle effects could not be separated from the effects of larger particles.[34] Among Medicare enrollees from 59 US counties between 1999 and 2005, Chang and colleagues[35] found a positive association between coarse PM and same-day admissions for cardiovascular diseases. Chen and colleagues[36] found associations for fine but not coarse PM with mortality in the Chinese cities of Beijing, Shanghai, and Shenyang. Ongoing EPA-supported controlled human exposures studies are evaluating whether differing components of coarse particles modify their cardiovascular effects.

Update, 2010 to 2012: Acute and Chronic Cardiovascular Effects of Short- and Long-term Exposures to Ozone, Other Gaseous Pollutants, and OC

Until recently, evidence has been relatively scarce for independent associations of cardiovascular disease and short- or long-term exposures to gaseous pollutants such as ozone (O_3), oxides of nitrogen, and carbon monoxide (CO) except as markers for pollution sources and mixtures that also include particles. The possibility of teasing out the potential role of individual gaseous pollutants is limited in epidemiological studies that consider associations of cardiovascular risk with 1 pollutant at a time and do not consider those pollutants together in 1 model. However, in these studies, correlation among pollutants may limit inference on specific pollutant effects.

Separating out the individual and joint contributions of O_3 from particle mass of various sizes/compositions has been accomplished most successfully through controlled human and animal exposures (see below and the Table). Recent studies have begun to suggest that in addition to having adverse respiratory effects,[37] O_3 exposures may indeed have independent adverse cardiac sequella (see below).

NO_2, a secondary pollutant that often has regional and local sources, is often used as a marker for estimated exposure to a mix of pollutants, particularly from traffic. Independently of particle mass, its cardiovascular effects are less well established with certainty, although recent observational epidemiological studies often find it to be a predictor of adverse outcomes. CO is one of the most intriguing exposures. It has known cardiotoxic effects at levels that significantly increase carboxyhemoglobin levels, but at low doses, some investigators suggest that it may be cardioprotective against heart failure.[38] In their review of this topic, Constantin and colleagues[39] point out that the induction of hemoxygenase-1, leading to intrinsic CO, has been shown to be beneficial in vascular and lung transplantation and pulmonary hypertension models, in part through inhibition or modulation of inflammatory, apoptotic, and proliferative processes. Although most epidemiological studies link even low levels of CO to adverse effects, in those studies, CO is likely to be a marker for traffic.

Epidemiological studies of cardiovascular effects of OC continue to focus on measures of particulate OC without speciation, in great part because of its expense. Thus, data on the effects of specific volatile organic compounds on health outcomes are still lacking. Recent data support a specific role for OC particle components or their biogenic sources (eg, traffic, wood burning, restaurant emissions; the Table).

Short-term Exposures/Acute Effects

A recent controlled human exposure study has shown that O_3 can cause an increase in vascular markers of inflammation

and changes in markers of fibrinolysis and markers that affect autonomic control of heart rate and repolarization.[17] A German repeated measures observational study found that heart rate and repolarization changes were associated with increased O_3 levels in subjects considered sensitive because of specific genetic polymorphisms or chronic disease (type 2 diabetes mellitus).[16] The Canadian Health Measures Survey found increased O_3 to be predictive of increased resting heart rate and blood pressure and reduced exercise tolerance in adults.[19] These findings provide biological plausibility for the recent epidemiology studies that associate short-term O_3 exposures with cardiovascular morbidity and mortality.

A large number of publications on epidemiological studies associating short-term increases in ambient gases with cardiovascular outcomes have appeared during the last 2 years. In studies not presenting models considering >1 pollutant at a time, associations of short-term increases in ambient gases and particles have been predictive of cardiovascular mortality or morbidity in the Po Valley of northern Italy (O_3, NO_2, $PM_{2.5}$)[21] and Seoul, South Korea (NO_2, CO, SO_2, PM_{10}; weaker associations with O_3).[22] When a maximum 8-hour average was used, an interquartile range increase of 2-day average O_3 predicted an increased risk of cardiovascular mortality of 4.5% (95% confidence interval, 1.4--7.5) that was more evident in the cool than in the warm season in Suzhou, China.[23] After adjustment for PM, short-term elevations in O_3 or NO_2 were associated with increased cardiovascular mortality or morbidity in studies from Prague (O_3),[24] the Pearl River Delta of southern China (O_3, NO_2),[25] and Lisbon, Portugal (O_3)[26]; a study of 10 Italian cities (NO_2)[27]; and the Public Health and Air Pollution in Asia Study, which evaluated health effects across large urban populations in 4 Asian countries (O_3, NO_2).[28]

Short-term exposures to particle pollution (including black carbon and OC) were associated with increases in blood pressure, whereas increases in O_3 were linked to blood pressure decreases in a repeated measures study of patients with type 2 diabetes mellitus.[18] In elderly subjects with coronary artery disease from the Los Angeles, CA, basin, exposure to primary components of fossil fuel combustion (eg, OC) was associated with ST-segment depression[39] and with elevated ambulatory blood pressure.[40] Associations of OC with higher blood pressure were of greatest magnitude among obese participants.

Long-term Exposures/Chronic Effects

Several recent large longitudinal cohort studies support the 2010 AHA conclusion that long-term particle mass exposures of traffic and nontraffic origin increase the risk of cardiovascular disease. Despite longitudinal decreases in $PM_{2.5}$ levels, in the Harvard Six Cities Study, investigators found a linear dose-response association of mortality with annual average $PM_{2.5}$ down to concentrations of 8 $\mu g/m^3$. Exposures to PM constituents or other ambient pollutants were not considered.[41] Long-term exposures to estimated residential $PM_{2.5}$ predicted increased blood pressure in a study in Germany.[42]

Recent studies also support the hypothesis that in real-world ambient pollution mixtures, both gases and particles contribute to long-term adverse cardiac effects. In the California Teachers Study, long-term exposure to PM_{10} was associated with elevated risks for IHD and incident stroke; exposure to nitrogen oxides was associated with elevated risk of IHD.[29] In a metropolitan Vancouver population of 45- to 85-year-old adults followed up for 5 years, increased long-term exposures to black carbon, a marker for traffic, predicted increased cardiovascular hospitalization after $PM_{2.5}$ and NO_2 were controlled for.[30] A study of long-haul truck drivers found that long-term exposures to elevated levels of ambient NO_2 predicted increased cardiovascular mortality, but associations were attenuated and not significant ($P<0.05$) in multipollutant models including $PM_{2.5}$, SO_2, and NO_2.[43] In a US study of 17 545 male health professionals, investigators found no associations of long-term PM exposures with cardiovascular mortality and hypothesized that this population may have been protected by healthier lifestyles and higher socioeconomic status.[44] In a study conducted in Shenyang, China, evaluating 12 years of data, long-term exposures to both PM_{10} and NO_2 predicted increased cardiovascular and cerebrovascular mortality.[31] In a Toronto study, after adjustment for multiple covariates, elevation of estimated long-term NO_2 exposures was significantly associated with increased IHD risk (relative risk, 1.33; 95% confidence interval, 1.2--1.47). Subjects living near major roads and highways had a trend toward an elevated risk of IHD (relative risk, 1.08; 95% confidence interval, 0.99--1.18). Regional $PM_{2.5}$ and O_3 were not associated with risk of IHD.[32]

An Increasing Source of Ambient Particles? Wildfire, Outdoor Biomass Burning, and Cardiovascular Outcomes

In the past decade, we have had bursts of large wildfires in the United States and worldwide, with short-term increases in ambient particle mass levels that can exceed those produced by traffic industrial sources in the United States and can be transported worldwide.[45] Some scientists project that future climate and its changes will play a significant role in driving global fire trends. Bush fires in Australia[46] and forest fires (independently of urban pollution) in Athens[47] have been associated with increased cardiovascular and respiratory mortality. In Brazil, burning of outdoor biomass (sugar cane) was associated with an increase in hospital admissions for hypertension.[48] The investigators suggested that these findings might have relevance for cardiovascular responses to the burning of sugar cane--derived ethanol, a primary source of automobile fuel in Brazil.

Update, 2010 to 2012: Biological Mechanisms for the Effects of Pollutant Exposures on Atherosclerosis or Thrombus Formation

In nonsmoking Belgian adults with diabetes mellitus, each doubling of home distance from major roads was associated with a decrease in oxidized low-density lipoprotein, a risk factor for atherosclerosis.[49] Coronary artery calcification and carotid intima-media thickness are 2 measures of subclinical atherosclerosis that have been considered in recent studies of long-term cardiovascular effects.[50] In a follow-up to the first cross-sectional study demonstrating an association of higher estimated levels of increased carotid intima-media thickness with increased long-term exposure to $PM_{2.5}$,[51,52] a population-based German study of >4000 adults found an association of

increased carotid intima-media thickness and increased blood pressure with increased exposures to estimated long-term $PM_{2.5}$ and distance to high traffic.[42,53] A Danish study showed that living in city centers was associated with increased coronary artery calcification, but whether this association is due to increased pollution exposure is not known.[54] Studies supporting a role for particles in increasing the risk of thrombus formation have recently been reviewed.[55] In healthy volunteers, particle traps were shown to reduce thrombogenicity of diesel exhaust.[56]

Update, 2010 to 2012: Susceptibility and Vulnerability

The literature on susceptibility or vulnerability to particulate pollution has been summarized recently.[57–60] Sources of susceptibility considered in our review include genetics, life stage or age, sex, preexisting chronic conditions (diabetes mellitus, obesity, cardiovascular disease, chronic obstructive pulmonary disease), adverse weather conditions, and acute infections (eg, influenza).[61] As stated by the EPA (2009 Particle Matter EPA Integrated Science Assessment, Chapter 8 [http://www.epa.gov/ncea/isa]), lower socioeconomic position can be viewed both as a source of vulnerability (with increased absolute exposure to higher levels of pollution) and as a source of susceptibility (with increased disease at a given exposure because of susceptibility cofactors such as stress or lack of access to health care).

Genetics

Evaluation of genetic susceptibility to air pollution has been used as a tool for exploring mechanisms and pathways for cardiovascular effects and may contribute to understanding the distribution of risk. In a recent systematic review, Zanobetti and colleagues[62] found 16 articles evaluating gene--air pollution interaction and cardiovascular disease. These articles were based on 3 study populations: the Normative Aging Study (NAS),[63–75] the Air Pollution and Inflammatory Response in Myocardial Infarction Survivors: Gene-Environment Interaction in a High Risk Group (AIRGENE),[76,77] and MESA.[78] These studies have focused on individual functional polymorphisms or candidate genes in pathways related to oxidative stress, inflammation, endothelial function, and the angiotensin pathway. Although all 3 studies point to the importance of these pathways, the studies have differed substantially in both the cardiovascular outcomes and polymorphisms examined, with little work on replication of individual study findings. Except for blood pressure, most of the outcomes evaluated in these studies are subclinical (eg, heart rate variability, inflammatory biomarkers) and usually, although not always, are considered in relation to relatively short-term exposures. Although they inform our understanding of pathways through which pollution perturbs the system, investigators have yet to assess the relevance of these findings for the definition of susceptibility to pollution effects on the development of atherosclerosis and clinical cardiovascular morbidity and mortality.

Studies of cardiovascular effects of pollution in the apolipoprotein E knockout murine model (characterized by oxidative stress and vulnerability to atherosclerosis) support the role of oxidative stress genes in increasing susceptibility to chronic cardiovascular effects of pollution.[57,79] The importance of oxidative stress genetic polymorphisms is also supported by consistent findings in the adult and pediatric respiratory literature that highly prevalent polymorphisms in glutathione S-transferases may increase pollution- or smoking-related risk of reduced lung function and increased wheeze and pulmonary inflammation.[80–92] To the extent that pulmonary oxidative stress and inflammation increase systemic inflammation and cardiovascular risk, these findings have relevance for cardiovascular susceptibility to pollution. As Zanobetti and colleagues[62] point out, although replication is needed to draw stronger conclusions, a critical issue is whether between-study replication should be done by single-nucleotide polymorphism or by pathway. Although new pathways related to genetic sources of cardiovascular susceptibility to pollution may come from genome-wide association studies, they will require cooperation and pooling across studies, which is currently being fostered by the European Union in the European Study of Cohorts for Air Pollution Effects (ESCAPE). Using their genome-wide association study data, the Framingham Heart Study has recently created a Genetic Risk Score comprising 13 single-nucleotide polymorphisms associated with coronary disease that provides modest risk reclassification for risk of incident cardiovascular disease (defined as general cardiovascular disease [cardiovascular death, myocardial infarction, coronary insufficiency, angina pectoris, stroke, transient ischemic attack, intermittent claudication, or congestive heart failure] or "hard cardiovascular disease" [coronary death or myocardial infarction]) and improves discrimination for high coronary artery calcium.[93] Genetic risk scores known to predict cardiovascular risk can also be applied to the evaluation of cardiovascular susceptibility to pollution. Epigenetic changes[71,94–96] and atherosclerosis are less well-understood mechanisms that are being evaluated as mediators of chronic effects of long-term pollution exposures on clinical cardiovascular outcomes.

Life Stage

Older age is a strong risk factor for cardiovascular disease, and risk factors for coronary artery disease vary by age,[97] but the literature is not consistent in finding that age >65 or 75 years increases susceptibility to the effects of pollution on clinical cardiovascular events.

Sex

Women have a lower lifetime risk of cardiovascular disease than men.[97] The literature on sex as a source of vulnerability to pollution cardiovascular effects is sparse with conflicting findings. While some studies suggest that associations of $PM_{2.5}$ or $PM_{10-2.5}$ with cardiovascular-related mortality are higher for women than for men,[57,98,99] other studies suggest no sex differences or (for PM_{10}), increased vulnerability in men. Many of the administrative studies suffer from a lack of access to data on other risk factors that may be confounders or to data for women on menopausal status, which may modify risk.

Race/Ethnicity

Differences in risk factor burden (cholesterol level, blood pressure, smoking status, and diabetes status) resulted in marked

differences in lifetime risk of cardiovascular disease that were consistent across race (black versus white) and birth cohorts in a recent meta-analysis at the individual level using data from 18 cohort studies involving 257 384 men and women.[97] Studies on race/ethnicity as a source of susceptibility to pollution are inconsistent in their findings, and many are flawed in the level of information available about risk factor burden, which may account for heterogeneity of findings on susceptibility. In addition, the terms "Hispanic" and "Latino" represent a large population that is highly variable in terms of diet, country of origin, genetic background, sources of stress, and many other underlying factors that may themselves be sources of susceptibility.[100]

Socioeconomic Position

Methods for defining sources of susceptibility to environmental risk in populations in positions of economic or social inequity were recently discussed thoroughly in a series of 3 articles published in the *American Journal of Public Health*.[58–60] Environmental justice is a goal in regulating pollution. Environmental justice is defined by the US EPA (http://www.epa.gov/oecaerth/environmentaljustice/index.html) as follows:

> The fair treatment and meaningful involvement of all people regardless of race, color, national origin or income with respect to the development, implementation and enforcement of environmental laws, regulations and policies. Fair treatment means that no group of people, including racial, ethnic or socioeconomic group should bear a disproportionate share of the negative environmental consequences resulting from industrial, municipal, and commercial operations or the execution of federal, state, local and tribal programs and policies.

Clinical cardiovascular risk can aggregate in poor neighborhoods because of multiple interacting sources of vulnerability or susceptibility that are related to socioeconomic disadvantage (eg, increased absolute levels of air pollutants, stress, interacting toxicants, obesity, diabetes mellitus, smoking, hypertension, differences in nutrition, lack of safe places to exercise, and many other environmental coexposures).

Preexisting Chronic Conditions: Diabetes Mellitus and Obesity

The obesity epidemic and associated cultural changes in activity and diet have led to an increase in type 2 diabetes mellitus, which many (but not all) studies suggest increases susceptibility to adverse cardiovascular effects of temperature[101] and pollution.[102] Many studies have suggested that people with type 2 diabetes mellitus may be more vulnerable to the acute effects of particles on blood pressure and other vascular responses.[18,103] As discussed in our 2008 review,[102] diabetes-associated chronic inflammation and oxidative stress may quench nitric oxide, create imbalances in vasoactive mediators in arterial tissue, change smooth muscle responsiveness as a result of chronic autonomic dysfunction, or impair flow-mediated dilation as a result of vascular remodeling. Animal models support obesity and diabetes mellitus as sources of vulnerability to cardiovascular effects of particle mass: Exposure to $PM_{2.5}$ increased the risk of insulin resistance in rats fed a high-fat diet but not in those fed a normal-chow diet.[104] Data on obesity without diabetes mellitus as a source of pollution susceptibility are less consistent.[57] In the Women's Health Initiative, the association between cardiovascular events and the level of $PM_{2.5}$ increased with higher body mass index and waist-to-hip ratio, but other studies have not found effect modification by obesity without diabetes mellitus.[105]

Preexisting Chronic Conditions: Chronic Obstructive Pulmonary Disease

Perhaps because of the heterogeneity of the disease and because of the high rate of misclassification of chronic obstructive pulmonary disease when administrative data are used, studies are not consistent in finding chronic obstructive pulmonary disease as a source of susceptibility to cardiovascular effects of pollution.[106,107] As chronic obstructive pulmonary disease is classified more carefully and specifically, there will be better opportunity to evaluate the susceptibility of people with chronic obstructive pulmonary disease.

Temperature, Pollution, and Cardiovascular Risk

Meteorological conditions influence the production of secondary pollutants such as ozone and nitrogen dioxide and dictate the long-range transportation of pollutants (www.epa/oar/caa). In the past, studies of the cardiovascular effects of pollution have been reported separately from studies of cardiovascular effects of weather (eg, temperature, humidity), even though they are often intertwined. Hot and cold temperature extremes have been linked to acute cardiovascular events,[108] and accumulating evidence suggests dose-response relationships that may not relate just to the extremes and may relate in part to transitions/variability in temperature and socioeconomic or physiological issues related to adaptation.[109] For example, heat waves have been demonstrated to increase cardiovascular mortality,[110] especially in the populations unable to adapt physiologically (the elderly) or to acquire air conditioning or protective housing.[101,111–114] Using a case-crossover study design, California researchers observed an increased risk of hospitalization for IHD, ischemic stroke, and heat stroke with a 10°F increase in same-day apparent temperature.[115] Ownership and use of air conditioners significantly reduced the effects of temperature on these outcomes after controlling for potential confounding by family income and other socioeconomic factors.

Low temperature was linked to incident acute myocardial infarction in a large German study.[108] The first annual extreme cold event was associated with increased emergency room visits for circulatory diseases in a Taiwan study.[116] In a recent Dutch study, lower temperature was a predictor of higher incidence of acute myocardial infarction and acute presentation for abdominal aortic aneurysms.[117]

A limited number of studies have looked simultaneously at ambient temperature, pollution, and their interaction in increasing the risk of adverse cardiovascular outcomes. A repeated measures study of adults with type 2 diabetes mellitus conducted in Boston demonstrated opposing effects of fine particle mass compared with the effects of high temperature or ozone.[18] Whereas increases in $PM_{2.5}$ were associated with elevated systolic and diastolic blood pressures, higher temperature and higher ozone levels were linked to a reduction in blood

pressure, particularly in those whose mean blood pressure was already within normal limits. Heart rate variability was most reduced when both temperature and ozone were high in the Boston Normative Aging Study.[118] In Wuhan, China, where the average daily temperature in July is 37.2°C and the maximum daily temperature often exceeds 40°C, investigators found that increases in PM_{10} increased the risk of mortality resulting from cardiovascular disease and stroke and that increased temperature increased susceptibility to particle-related mortality.[119] In this study, elevated levels of NO_2 and SO_2 (but not ozone) were also associated with increased mortality.

Infection

Low temperature is linked to low humidity in some urban environments, and low humidity has been linked to increases in influenza.[120] In a recent time-series study of daily mortality and hospital admissions in Hong Kong, interactions were found between influenza activity (measured by viral surveillance) and air pollution in the estimated risks for respiratory disease, particularly for ozone.[36] A recent *Lancet* review demonstrated the role of influenza not only as a cause of myocarditis but also as a trigger for acute myocardial infarction or death resulting from cardiovascular disease.[121] It remains to be seen whether influenza-associated cardiovascular outcomes are modified by pollution levels or by changes in temperature, humidity, or other weather-related exposures.

Protection Against Cardiovascular Effects of Pollution

The incremental risk of cardiovascular disease to any individual associated with air pollution exposure may appear low. However, because large populations are simultaneously exposed, the absolute impact in terms of the number of excess cardiovascular events and years of healthy life lost at the population level is very large,[122,123] increasing its importance as a public health problem.

Reduction of pollution exposure and the adverse cardiovascular effects of pollution is likely to come from a series of personal and community actions and from public policy measures.[124] Investigators should take advantage of large cardiovascular clinical trials to assess whether factors that improve the risk of cardiovascular disease also reduce pollution effects on cardiovascular risk. Specifically, reduction of the cardiovascular effects of pollution may come from cessation of smoking, control of blood pressure, and control and reduction of the risk of obesity and diabetes mellitus. Lowering lipids and reducing stress may also reduce pollution-associated risk.

Because of confounding by indication in observational studies, it is often difficult to evaluate whether medications used to lower lipids or to control blood pressure alter the adverse effects of air pollution effects, but some study designs (eg, randomized trials and controlled human exposure studies) may give insight into whether specific foods, micronutrients, vitamin D, omega-3 fatty acids, or methyl donors are protective against cardiovascular effects of pollution in vulnerable populations. If pollution interacts with influenza to increase cardiovascular death during influenza season, then vaccination against influenza (which is recommended in any case) may further reduce adverse pollution effects.

Definitive evidence is currently lacking on whether specific lifestyle or pharmacological interventions lower the relative risk associated with air pollution exposure. In most studies, the relative risk of cardiovascular disease associated with air pollution exposure appears constant regardless of the presence of underlying risk factors for cardiovascular disease, with the few exceptions reviewed above. There is ample evidence that primary and secondary prevention measures such as control of blood pressure and lipids, smoking cessation, habitual physical activity, and dietary patterns such as the Dietary Approaches to Stop Hypertension diet reduce the baseline risk of cardiovascular disease. Thus, it follows that evidence-based prevention strategies should lower the absolute risk of cardiovascular disease associated with air pollution. This implies that with effective primary and secondary prevention measures, there will be a smaller number of excess cases of cardiovascular disease resulting from exposure to air pollution. An important consideration is that focusing on individual-level behaviors as a primary driver of risk mitigation raises issues of environmental justice; not all populations are equally or equitably exposed to air pollution or have access to the resources to engage in the primary and secondary prevention measures known to be effective.[124]

Community and individual adaptive behaviors (eg, staying indoors during declared pollution episodes or heat waves, using air conditioning, and closing windows and doors) may be helpful but come at a price (increased energy consumption), may not be within economic reach of the poorest or most vulnerable populations, and may not be under the control of elderly people with dementia or with diminished perception of changes in temperature.

In this follow-up to the 2010 AHA Scientific Statement,[1] we have presented an update on studies of the effects of pollution and climate on cardiovascular outcomes. Study results on the health effects and costs of air pollution and extreme meteorological conditions should be disseminated not only to the scientific and regulatory communities but also to the general public and their administrative servants in language that is clear and objective. Such efforts will contribute to the setting and implementation of air quality standards designed to protect not only the general public but also its most vulnerable citizens.

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None.

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Key Words: AHA Medical/Scientific Statements ■ air pollution ■ cardiovascular diseases ■ epidemiology ■ prevention